Finally, Applicants submit herewith as a separate paper an Information Disclosure Statement ("IDS ") listing references cited by an opponent in an opposition proceeding to the European counterpart of the present application.

OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS

The Examiner rejected 1) claims 9 and 10 under the judicially created doctrine of obviousness-type double patenting over claim 13 of U.S. Patent No. RE37302 and 2) claims 11-14 as being unpatentable over claim 13 of U.S. Patent No. RE37302 in view of Campbell.

In response, Applicants note that while claims 9-14 have been cancelled without prejudice, Applicants address this rejection as it may be applied against pending claims 15-20. In particular, Applicants address the rejection of claims 11-14 as being unpatentable over claim 13 of U.S. Patent No. RE37302 in view of Campbell as it might be applied against added claims 15-20.

In this regard, Applicants submit herewith a terminal disclaimer over U.S. Patent No. RE37302 and note that the "filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting and raises neither a presumption nor estoppel on the merits of the rejection". Quad Environmental Technologies Corp. v. Union Sanitary District, 20 USPQ 2d 1392 (Fed. Cir. 1991).

In the absence of U.S. Patent No. RE37302, the sole remaining prior art is Campbell, which describes the use of the combination of metformin and sulfonylureas in the treatment of diabetes. However, as Campbell neither teaches nor suggests the combination of GLP-1 and metformin in the treatment of diabetes, Applicants respectfully request withdrawal of the obviousness-type double patenting rejection of claims 11-14 as it may be applied against pending claims 15-20.

REJECTION OF THE CLAIMS UNDER 35 USC 112, SECOND PARAGRAPH

The Examiner rejected claims 12 and 14 as being indefinite because they are improperly dependent.

In reply, Applicants submit that this rejection is rendered moot by the cancellation of claims 12 and 14 without prejudice.

REJECTION OF THE CLAIMS UNDER 35 USC §102(b)

The Examiner rejected claim 9 as anticipated by the disclosure in Kabadi et al of the treatment of type I diabetes using the combination of insulin and the sulfonylurea tolasamide. Insulin was applied as an analogue of GLP-1 because it has a single amino acid in common with GLP-1.

In reply, Applicants respectfully submit that this rejection is rendered moot by the cancellation of claim 9 without prejudice.

REJECTIONS OF THE CLAIMS UNDER 35 USC §103(a)

A. Claims 9 and 10 were rejected as unpatentable over Buckley et al. (WO 91/11457) in view of Parker et al. (Diabetes 40:Supp. 1, Abstract 847) and as unpatentable over Habener (WO 90/11296) in view of Parker because it would be obvious to combine the GLP-1 peptides as taught by Buckley or Habener with the oral hypoglycemic agent glibenclamide since Parker teaches that GLP-1 (7-37) and glibenclamide had an additive effect on insulin secretion.

In reply, Applicants submit that the above rejections are rendered moot by the amendments to the claims presented herein.

B. Claims 11-14 were rejected as unpatentable over Buckley et al. (WO 91/11457) and Parker et al. (Diabetes 40:Supp. 1, Abstract 847) or Habener (WO11296) and Parker as applied to claims 9 and 10, and further in view of Ramachandran et al. (Diabete Metabolisme 13(2):140-141, 1987). While claims 11-14 have been cancelled without prejudice, Applicants address this rejection as it may be applied against pending claims 15-20.

The Examiner cites to Habener and Buckley as teaching analogs and derivatives of GLP-1 useful in the treatment of diabetes; Parker as teaching that the combination of GLP-

1 (7-37) and glibenclamide had an additive effect on the amount of insulin secreted from HIT cells in vivo; and Ramachandran as teaching that the combination of glibenclamide and metformin is effective in the treatment of diabetes. The Examiner therefore concludes:

> "It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the oral hypoglycemic metformin as taught by Ramachandran et al to the glibenclamide treatment method as combined *supra* because Ramachandran et al teaches that the combination of the oral hypoglycemic agents glibenclamide and metformin are effective in the treatment of diabetes and Parker et al teach that when GLP-1 (7-37) and glibenclamide (ie. an oral hypoglycemic agent) are combined, the agents had an additive effect on the amount of insulin secretion and therefore the combination of all three agents[1] would be reasonably expected to be useful in the treatment of diabetes" (pages 7 and 9 of Office Action).

Applicants respectfully traverse this rejection as it may be applied to pending claims 15-20.

"To establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was claimed" [In re Kotzab, 554 USPQ2d 1308, 1316 (Fed. Cir. 2000), emphasis added]. Of course, it is well settled that the prior art references must be viewed without the benefit of hindsight afforded by the inventor's disclosure [In re Paulsen 31 USPQ 2d 1671,1674 (Fed. Cir.1994)] and that "obvious to try" is not the proper standard for obviousness [In re O'Farrell 7 USPQ2d 1673,1681 (Fed. Cir. 1988)].

Here, the Examiner's rejection is based on the assertion that because the combinations of 1) GLP-1 and glibenclamide (Parker) and 2) metformin and glibenclamide (Ramachandran) are allegedly taught by the prior art to be useful for a common purpose (treatment of diabetes), it would be prima facie obvious to one skilled in the art to combine GLP-1 and metformin for the same purpose.

With all due respect, Applicants disagree.

---

1 Applicants assume that the Examiner meant that the combination of two of the three agents (GLP-1 and metformin) disclosed in Parker and Ramachandran would be reasonably expected to be useful in the treatment of diabetes.

First, Applicants submit that the Examiner's characterization of the Parker reference is incorrect.

Parker does not teach that the combination of GLP-1 (7-37) and glibenclamide had an additive effect on the amount of insulin secreted from HIT cells in vivo. Rather, Parker describes experiments conducted on HIT or islet cells in vitro to compare the effects of GLP-1 and glibenclamide on insulin secretion.

More importantly, the design of the experiments conducted by Parker makes it impossible to draw any conclusions about the possible effects of the combination of GLP-1 and glibenclamide on insulin secretion from cells in vitro, yet alone that the combination would be a useful in vivo therapy for subjects with diabetes.

In particular, Parker describes 3 different sets of experiments:

1) islets were perifused with 8 mM glucose alone or with 8 mM glucose and either GLP-1 or glibenclamide;

2) HIT cells were incubated in glucose-containing or glucose-free media with either glibenclamide or GLP-1; and

3) Islets were statically incubated in 8 mM glucose with GLP-1 or in 8 mM glucose with GLP-1 plus glibenclamide.

In the first two sets of experiments, the cells were not incubated with the combination of GLP-1 and glibenclamide while in the third experiment, the cells were incubated with the combination but not with glibenclamide alone. Thus, Parker does not present a single experiment in which the two drugs were each administered alone and then in combination[2].

In the absence of such an experiment, Applicants submit that it is not scientifically possible to draw any conclusions about what effects, if any, the combination of GLP-1 and glibenclamide might have on insulin secretion from cells in vitro, yet alone in vivo.

It is therefore Applicants' position that as of the 1992 priority filing date of the present application, the use of GLP-1 in combination with another drug for the treatment of diabetes had neither been disclosed nor suggested by the prior art. Indeed, a review of the literature published in the time period at or around 1992 reveals that the interest in GLP-1 was in its use

---

2 While the first and third sets of experiments utilized the same cell type (islets), one cannot extrapolate from the results obtained with testing of either drug alone in the first experiment to the results obtained from testing of the combination in the third experiment as the conditions (perifusion versus static administration) under which the first and third experiments were carried out are completely different.

as a monotherapy and not as a combination therapy. For example, Nathan et al [Diabetes Care (1992) 15:270-276; copy provided with accompanying IDS filed herewith], in discussing the ability of naturally occurring GLP-1 (7-37) to stimulate insulin secretion in type II diabetics without producing hypoglycemia, conclude that GLP-1 could be exploited as an alternative to sulfonylureas in the treatment of type II diabetes (see the last paragraph of page 275 of Nathan et al).

Second, even assuming arguendo that the combinations of 1) GLP-1 and glibenclamide (Parker) and 2) metformin and glibenclamide (Ramachandran) were taught by the prior art to be useful for the treatment of diabetes, Applicants submit that the Examiner's allegation that the motivation to selectively pick GLP-1 and metformin from the alleged Parker and Ramachandran combinations respectively and then combine them comes from knowledge of one skilled in the art (since no express teaching or suggestion is provided by prior art) begs the question of why, if this combination was so obvious to those of skill in the art, that no one suggested this combination prior to the present inventors.

In particular, Applicants note that while the use of metformin in the treatment of diabetes dates to 35 years before the 1992 priority filing date of the present application (see last paragraph of page 33 of the Campbell reference cited by the Examiner) and the use of GLP-1 to at least 5 years [see Kreymann et al (1987) Lancet II: 1300-1304; copy attached] before the priority filing date, the literature is conspicuously silent as to any suggestion or motivation to combine GLP-1 with another drug for the treatment of diabetes.

In this regard, Applicants note that the combination of any two drugs carries with it the inherent risk of adverse interactions between the two drugs as well as exposing the patient to the side effects associated with each drug. Here, since GLP-1 is a naturally occurring substance that successfully stimulated insulin secretion without producing a serious side effect (hypoglemia) associated with other diabetes drugs (see Nathan et al, cited above) and results in very efficacious lowering of blood glucose, there was no motivation to combine GLP-1 with other drugs.

Finally, Applicants direct the Examiner's decision to In re Geiger 2 USPQ 2d 1276 (Fed. Cir. 1987), copy attached.

In Geiger, the claim at issue was directed to a method of inhibiting scale corrosion on, and corrosion of metal parts in, cooling water systems by use of compositions containing 1) a

sulfonated styrene/maleic anhydride copolymer, 2) a water soluble zinc compound, and 3) an organo-phosphorus acid compound or water soluble salt thereof.

Based upon the prior art and the fact that each of the three components of the composition used in the claimed method was conventionally employed in the art for treating cooling water systems, the Board of Patent Appeals and Interferences held that "it would have been prima facie obvious .....to employ these components in combination for their known function" Geiger at 1278.

On appeal to the Federal Circuit, the applicant argued that "the PTO's position represented hindsight reconstruction or, at best, established that it would have been 'obvious to try' various combinations of known scale and corrosion prevention agents, including the combination recited in the appealed claims" Id. The Federal Circuit agreed with the applicant and reversed the Board's finding of obviousness. In so holding, the Federal Circuit found that the cited art provided no suggestion to combine the three components and concluded:

"At best, ... one might find it obvious to try various combinations of these known scale and corrosion prevention agents. However, this is not the standard of 35 U.S.C. 103." Id.

Here, even assuming arguendo that the combinations of 1) GLP-1 and glibenclamide (Parker) and 2) metformin and glibenclamide (Ramachandran) were taught to be useful for the treatment of diabetes, the claimed method of treatment (of diabetes), as in Geiger, utilizes a combination of components (in the present case, GLP-1 and metformin) that were known individually in the art to be useful in the indicated treatment. In addition, here, as in Geiger, the Patent Office is asserting that because each component (GLP-1 and metformin) was known to be employed for a common function (treating diabetes), it would be prima facie obvious to employ the components in combination for the same function.

However, here as in Geiger, there was a complete absence of any suggestion in the literature to combine the specific molecules recited in the present claims and other agents such as thiazolidinediones, the non-sulfonylurea insulin-releasing drug N-[(trans-4-isopropylcyclohexyl)-carbonyl]-D-phenylalanine (A-4166), glucosidase inhibitors (acarbose), glucagon antagonists, potasium channel openers, hepatic enzyme inhibitors, glucose uptake modulators, compounds modifying the lipid metabolism (fibrins, statins), compounds lowering food intake, and agents acting on the ATP-dependent potassium channel of the ß-cells [see, for example, Sohda et al (1992) J.Med.Chem., 35:2617-2626, which discloses thiazolidinediones; and Sato et al (1991) Diabetes Res. Clin. Pract., 12:53-59, which

discloses the non-sulfonylurea insulin-releasing drug N-[(trans-4-isopropylcyclohexyl)-carbonyl]-D-phenylalanine (A-4166)], were known as of the priority filing date of the present application to be available for the claimed treatment method. Applicants therefore submit that the Examiner in the present application (like the Board in Geiger) is relying on impermissible hindsight to pick and choose among the agents known at the time of filing of the present application to be useful in the treatment of diabetes to arrive at the claimed combination and at best, is applying an "obvious to try" standard that has long been held not to be the proper standard for obviousness.

Accordingly, in view of Geiger and in view of the above arguments, Applicants respectfully request withdrawal of the 103 rejections as they may be applied to added claims 15-20.

In sum, in view of the above amendments and remarks, it is respectfully submitted that all claims are in condition for allowance.

Early action to that end is respectfully requested.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: August 6, 2002

Richard W. Bork, Reg. No. 36,459
Novo Nordisk of North America, Inc.
405 Lexington Avenue, Suite 6400
New York, NY 10174-6401
(212) 867-0123

"Marked-Up" Copy of Amendments to the Specification

Please replace the paragraph at page 1 after the title with the following paragraph:

--CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application no. 08/842,121 filed on April 23, 1997, now abandoned, which is a continuation of 08/295,913 filed on October 13, 1994, which [now] issued as patent 5,631,224 [issued] on October 28, 1998, and is now reissued as reissue patent RE 37,302 on July 31, 2001, which is a 371 national application of PCT/DK93/00099 filed on March 18, 1993, which claims priority to Danish application 363/92 filed March 19, 1992, the contents of which are fully incorporated herein by reference. - -